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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/914,651 | 12/27/2001 | Peter Laurence Molloy | 50179-093 | 9660 |
| 20277 | 7590 | 11/19/2003 | EXAMINER | |
| MCDERMOTT WILL & EMERY 600 13TH STREET, N.W. WASHINGTON, DC 20005-3096 | | | | LEFFERS JR, GERALD G |
| ART UNIT | | PAPER NUMBER | | |
| | | 1636 | | |

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|---------------------------------------|---------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/914,651 | MOLLOY ET AL. |
| | Examiner Gerald G Leffers Jr., PhD | Art Unit 1636 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 27 August 2003.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 54-106 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 54-106 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) The translation of the foreign language provisional application has been received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

| | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) <i>1/2/03</i> Paper No(s) <i>1/2/03</i> <i>and 8/2001</i> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (claims 54-94) in the response filed 8/27/03 is acknowledged. The traversal is on the ground(s) that each of the inventions has the same special technical feature (i.e. they all involve the usage of a regulatory element derived from intron 3 of the PSM gene). This argument is found persuasive. The claims of Groups II-IV have been rejoined with claims 54-94. Claims 54-106 are pending and under consideration in the instant application.

Specification

The attempt to incorporate subject matter into this application by reference to O'Keefe et al (Biochimica et Biophysica, Vol. 1443, pages 113-27, 1998; see the entire reference, especially Accession No. AF007544) is improper because the nucleic acid sequence represented by AF007544 is essential matter. The incorporation of essential material in the specification by reference to a foreign application or foreign patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claim Objections

Claim 61 is objected to because of the following informalities: it is dependent upon a subsequent claim, which is improper. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 54-59, 63-67, 72-78, 85, 90-95 and 100-106 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims are all broadly drawn to “regulatory elements” derived from the 3rd intron of the PMSA gene described by O’Keefe et al. Claims 60-62, 68-71, 79-84, 86-89, 96-99 all recite that the regulatory element is an enhancer. Thus, the claims reasonably encompass other types of “regulatory elements” such as repressor sequences, RNA destabilization/stabilization sequences, etc. The instant specification, however, describes the instant invention solely in the context of enhancer elements obtained from intron 3 of the PMSA gene. Therefore, there is no basis for the skilled artisan to envision those embodiments that are not enhancer elements. The skilled artisan would have concluded, for this reason, that applicants were not in possession of the broadly claimed compositions and methods.

Claims 85-106 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* embodiments directed to expression of a desired polypeptide sequence, does not reasonably provide enablement for *in vivo* embodiments wherein the claimed regulatory elements are used to direct expression of a given heterologous sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The invention is extraordinarily complex, encompassing the use of novel transcriptional regulatory elements to drive expression of a therapeutic nucleic acid sequence in a given host such that efficacious treatment is achieved. The only disclosed utility for *in vivo* embodiments of the claimed invention is for the therapeutic treatment of a disease or condition (e.g. cancer).

Breadth of the claims: The breadth of the claims greatly exacerbates the complexity of the invention. The broadest claims encompass any disease or condition (e.g. any cancer). The claims encompass the use of any gene sequence or antisense sequence to achieve a therapeutic effect.

Guidance of the specification/The existence of working examples: The specification provides *in vitro* working examples that demonstrate multiple constructs obtained from the 3rd intron of the PMSA gene can demonstrate enhancer effects with different promoters. Guidance with regard to specific cancers, treatment regimens, heterologous sequences, etc., is only general in nature.

State of the art/Predictability of the art: The prior art appears to be silent with regard to the use of the specific enhancer elements taught in the instant specification. Thus, the prior art does not offset the deficiencies of the instant specification with regard to enabling the full, broadly claimed scope of the invention.

In general, gene therapy is a highly unpredictable and undeveloped field and the skill in the art is high. See Orkin et al (U) which states (page 1):

2. While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.

3. Significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host.

The consensus scientific opinion is that gene therapy was and still is highly unpredictable as evidenced by Orkin et al. The teachings of Verma et al (V), two years after the Orkin et al publication, reaffirm the teachings of Orkin et al that, even after the two years, there is no evidence of how to use gene therapy to predictably treat any disease. Verma et al teach

“Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story.” (Page 239, column 1). This reference teaches the considerable hurdles that must be overcome, including making sure that delivery of the gene gets to the right cells and getting enough of the gene delivered (page 239). This reference teaches that “The Achilles heel of gene therapy is gene delivery....Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression. Most of these approaches suffer from poor efficiency of delivery and transient expression of the gene.” (page 236, column 3). Palù et al (J. Biotechnol. (1999) 68: 1-13) teaches that despite hundreds of clinical trials underway, no successful outcome has been achieved (Palù et al, p. 1, Abstract). The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicates that most approaches suffer from poor efficiency and transient expression of the gene (p. 239, col. 3, 2nd paragraph). Likewise, Luo et al (Nature Biotechnology (2000) 18:33-37) indicates that non-viral synthetic delivery systems are very inefficient (e.g. see p. 33, Abstract and col. 1, 1st and 2nd paragraphs).

More recently, the most advanced clinical trial for the gene therapy treatment of severe combined immunodeficiency disease (SCID), the only disease for which has purportedly been “cured” by gene therapy, has been halted due to the development of cancer in two of the subjects. In both cases the retrovirus used to deliver the corrective gene to the patient inserted itself into a stretch of a gene associated with childhood leukemia (Nature, February 2003, Vol. 421, page 678, “Cancer fears cast doubts on future of gene therapy”).

Although the references cited above indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique. As recently as April of 1998 French Anderson (W) reviewed the status of the field of gene therapy and concluded that "Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease." (page 25, column 1). More recently, the most advanced clinical trial for the gene therapy treatment of severe combined immunodeficiency disease (SCID), the only disease for which has purportedly been "cured" by gene therapy, has been halted due to the development of cancer in two of the subjects. In both cases the retrovirus used to deliver the corrective gene to the patient inserted itself into a stretch of a gene associated with childhood leukemia (Nature, February 2003, Vol. 421, page 678, "Cancer fears cast doubts on future of gene therapy").

The amount of experimentation necessary: Given the factors outlined above, especially with regard to the high state of the art required to practice gene therapy, and the unpredictability of the art with regard to gene therapy in general, it would have required undue, unpredictable experimentation to practice the claimed invention in the full, broadly claimed scope encompassed by the rejected claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 54-106 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 54, 65, 72, 85, 95 recite the limitation of an enhancer or regulatory element “derived from” intron 3 of the PSM gene. It is unclear the nature and number of steps required in order to produce a “derivative” of intron 3 or the PSM gene. It would be remedial to use a term that does not imply an indirect method for producing the claimed regulatory element. For example, it would be remedial to amend the claim language to recite “obtained from”.

Claims 62-63, 69-71, 79-80, 87-89, 97-99 each recite a limitation regarding hybridization under “high stringency”. This term does not appear to be described in the specification as meaning a particular set of hybridization and is open to interpretation by the skilled artisan.

Claim 61 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term “the enhancer element” in claims 66 and 65, upon which claim 61 is dependent.

Claims 65-66 comprise the limitation that a particular element is “adjacent to” another in a nucleic acid sequence. The term is vague and indefinite in that it is not clear how close to another sequence an element has to be in order to satisfy the limitation of “adjacent to”. It would be remedial to amend the claim language to specify some sort of function linkage (e.g. operably linked).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

Gerald G. Leffers Jr.
GERRY LEFFERS
PRIMARY EXAMINER

Ggl